

### **REMARKS**

Claims 1, 7, 13, 15-17, 24 and 27-31 are pending in this application. Claims 7 and 13 are canceled herein without prejudice. Claims 1 and 15 are amended herein. Support for the claim amendments is provided by the specification at, e.g., page 9, lines 19-27 and by the claims as filed. Accordingly, no new matter is added by way of these amendments. Applicants respectfully request entry of the claim amendments and reconsideration in view of the following remarks.

#### **Formal Matters**

Applicants thank Examiner Fubara and supervisory Examiner Hartley for the courtesy of a telephonic interview on December 15, 2008 to discuss the claims and the cited documents of record, in particular the references of Li et al. Applicants thank the Examiners for their comments.

Applicants respectfully summarize the interview as follows. The discussion of the cited documents included Applicant's position that no *prima facie* case of obviousness is present. Examiner Hartley proposed certain claim amendments, including incorporating the limitations of claims 7 and 13 into claim 1, that were indicated to overcome the references to Li et al. and as likely to advance prosecution.

#### **Rejection Under 35 U.S.C. § 103**

Claims 1, 7 and 13 are rejected under 35 USC § 103(a) as allegedly unpatentable over Li et al. (*Polymer* (1997), **38**: 6197-6206) or Li et al. (*Polymer* (1998), **39**:3087-97). Claims 1, 7, 13, 24 and 29-31 are rejected under 35 USC § 103(a) as allegedly unpatentable over Li et al. (*Polymer* (1998), **39**:3087-97). Claims 15-17, 27 and 28 are rejected under 35 USC § 103(a) as allegedly unpatentable over Li et al. (*Polymer* (1997), **38**: 6197-6206) in view of Jarrett et al. (US 4,788,979) or Bays et al. (US 4,650,488). Applicants respectfully traverse the rejections.

Li et al. is said to teach dextrans grafted with poly-D,L-lactide. The Examiner acknowledges that Li et al. do not teach the separate D-lactide grafted form combined with the

separate L-lactide grafted form. The Examiner asserts that the combination of the D- and L-lactide grafted dextrans reads on the D,L-lactide grafted dextran of Li et al., because claim 1 does not include any special ratio of the L-lactide to D-lactide grafted dextrans. The Examiner asserts that one of skill in the art would incorporate the appropriate number of lactide monomers, as in claim 13, to obtain the desired release properties.

With respect to drug delivery, Li et al. is said to teach lactide polymers are useful to deliver hydrophilic molecules, such as peptides/proteins. The Examiner asserts that since the D,L-form contains both D- and L-lactides, one of ordinary skill in the art would have a reasonable expectation that both the combination of the D- and L-lactide grafted dextrans and the D,L-lactide grafted dextran of Li et al. alone would provide polymers with the anticipated *in vitro* degradation and controlled release properties. The Examiner acknowledges that Li et al. do not teach that the microspheres can be alternatively formulated as hydrogels. Nevertheless, the Examiner asserts that lactide and dextran hydrogels are known in the art, allegedly as evidenced by Graham et al. (US 4,814,182), and that one of skill in the art would formulate the composition as a hydrogel. Applicants must respectfully disagree.

To establish a *prima facie* case of obviousness, the Office must provide one or more references that, *inter alia*, teach or suggest all the limitations of the claimed invention. While the strict teaching - suggestion - motivation (TSM) test was rejected by the Supreme Court in *KSR v. Teleflex*, there still must be an “articulated reasoning with some rational underpinning to support the legal conclusion” of obviousness. *KSR International Co. v. Teleflex, Inc.*, 82 U.S.P.Q.2d 1385, at 1396 (S. Ct. 2007). Determining if there is an articulated reason requires analysis of a number of factors, including, e.g., whether there is evidence of teaching away and whether there is a reasonable expectation of success. Critical elements of the invention as a whole which clearly distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). In order for a combination of documents to defeat patentability, the Court in *KSR* held that the practitioner must have some reason to combine the elements in the way the claimed new invention does.

Solely to advance prosecution, the claims are amended herein to incorporate the limitations of claims 7 and 13 into claim 1, and claims 7 and 13 are canceled. As amended, the claims relate to hydrogel compositions comprised of a mixture of a dextran polymer grafted with homo-oligomers of L-lactic acid, and a dextran polymer grafted with homo-oligomers of D-lactic acid, wherein the homo-oligomers have 7-25 lactic acid monomers on average. As explained in the specification, the hydrogels of the instant invention may be provided by formation of a non-covalent interaction, i.e., a “stereocomplex”, between the homo-oligomers of L-lactic acid grafted onto one dextran polymer strand with the homo-oligomers of D-lactic acid grafted onto a separate dextran polymer strand.

Li et al. (1997, Vol. 38) describe the preparation of DSS (dextran sodium sulphate) and DEAED (diethylaminoethyl dextran chloride) grafted with D,L-poly(lactic acid) (PLA) at page 6200, Table 1. Other polymers are grafted with a mixture of PLA and poly(D,L-lactide-co-glycolic acid) (PLG). Li et al. (1998, Vol. 39) disclose the preparation of microspheres of the previously prepared polymers using a double emulsion method, and drug release from microspheres thus obtained. No hydrogels are taught by Li et al. in either reference, nor do Li et al. teach or otherwise suggest that the formation of a non-covalent interaction between the lactide oligomers to provide a “stereocomplex” is possible or that this property can be used to prepare a hydrogel.

Li et al. appear to have arrived empirically at satisfactory polymers for the formation of microspheres capable of controlled release. There is no suggestion that any improvement is needed or that there is any problem to be solved by altering the composition of the PLA or PLG oligomers grafted on the dextran polymer, nor is there any suggestion that the use of hydrogels would be desirable, or even equally effective to the microspheres described. Li et al. simply teach that certain specific polymers having significantly different chemical properties from those required by the instant claims were found to be useful to form microspheres capable of controlled release. Thus, as a preliminary matter, Li et al. in either reference provide no incentive to look to any other document for improvements, nor do these references provide any guidance as to what modifications should be made to produce any improvement.

As the Examiner has acknowledged, Li et al. do not teach the formation of dextran polymers separately grafted with D- and L-lactic acid homo-oligomers, or the formation of hydrogels at all, let alone hydrogels formed by non-covalent interactions between D- and L-homo-oligomers of lactic acid on separate dextran strands. Thus, the cited references fail to teach or suggest all the limitations of the invention as claimed.

Moreover, the Office has failed to provide a clearly articulated rationale that would have led one of ordinary skill in the art to combine and/or modify the teachings of the cited references to achieve the present invention. First, Applicants note that the separation of D,L-lactide into the individual enantiomers is a difficult and expensive process, and one of skill in the art would not automatically undertake the separation of the racemate without some clear reason to do so.

Second, even assuming for the sake of argument that one of ordinary skill decided for some reason to use either the pure D- or the pure L-lactide form, the Examiner has pointed to nothing in the cited art that would lead the artisan to prepare dextran polymers separately grafted with the D- and L-lactide homo-oligomers, and then to combine these polymers in an aqueous system in the same way that the claimed invention does to achieve the present result. Applicants respectfully submit that it would require a separate inventive step to utilize a polymer grafted with L-lactide homo-oligomers and a polymer grafted with D-lactide homo-oligomers in combination, and that this step is neither taught nor otherwise suggested by the cited art, alone or in combination.

The polymers of Li et al. were prepared by heating the appropriate dextran polymer and PLA in the presence of stannous octanoate to polymerize, then dissolving in methylene chloride and washing with water to remove unreacted polymer. See Li *et al.* (1997, Vol. 38) at p. 6198, col. 2. The resulting product is not a hydrogel, but rather a polymer that is soluble in organic solvent. See, e.g., 6199, col. 2, second paragraph: “The purified polymers are soluble in dichloromethane.”

Further, Li *et al.* (1997, Vol. 38) teach that high yields (>90%) are obtained after “residual amounts of unreacted DSS are removed **by exhaustive extraction with water** to obtain pure polymers.” See, e.g., 6199, col. 2, second paragraph (emphasis added). These results suggest

that the D,L-lactide grafted polymers of Li et al. are not soluble in water, i.e., the PLA grafts seem to be of such size that they control solubility over the dextran-type backbones. In addition, Li et al. teach that in the DSS- and DEAED-PLG polymers, “[t]he backbones *become water soluble* when most of the branches have been cleaved by hydrolysis.” See Li et al. (1998, Vol. 39), sentence bridging pages 3090-3091 (emphasis added).

In view of the teachings of Li et al. that D,L-lactide grafted dextran polymers are not water soluble, one of skill in the art would not have had a reasonable expectation of success that the D- or L-lactide grafted dextran polymers could be used to prepare hydrogel compositions, and would certainly not provide an expectation that the combination of a D-lactide grafted dextran and an L-lactide grafted dextran could be used to do so.

Moreover, the Office has failed to provide a clearly articulated rationale that would have led one of ordinary skill in the art to modify the microspheres of Li et al. in an attempt to form hydrogels. The Examiner has cited Graham et al. (US 4,814,182) as allegedly providing evidence that lactide and dextran hydrogels are known in the art, and by inference, that this somehow provides a rationale for one of skill in the art to modify the microspheres of Li et al. to provide hydrogels. Applicants note that the cited portion of Graham et al. lists dextran as a natural organic material which can be used as a cross-linkable biopolymer to form hydrogels, but does not mention lactide grafted polymers at all. See Graham et al., col. 2, lines 6-8. In addition, Graham et al. teach that chemically cross-linked (i.e., covalently linked) synthetic hydrophilic polymers are preferred. See Graham et al., col. 2, lines 52-56. By contrast, the hydrogels of the present invention are formed by a non-covalent “stereocomplex” interaction between the L-and D-lactide homooligomers on separate polymer strands.

Applicants respectfully submit that the disclosure by Graham et al. that hydrogels have been prepared from totally unrelated polymeric compositions provides neither an incentive nor a reasonable expectation of success that would have led one of ordinary skill to modify the teachings of Li et al. to achieve the invention as claimed. In addition, nothing in Graham et al. alters the

teachings of Li et al. that D,L-lactide grafted dextran polymers are water insoluble, and thus not suitable for hydrogels.

The deficiencies in the Office's *prima facie* case over Li et al., in either reference alone or in combination, are not addressed in view of Graham et al., or in combination with Bays et al. (US 4,650,488) and/or Jarrett et al. (US 4,788,979). Bays et al. describe an ear tube consisting partially of a water soluble material that may include poly(D,L-lactide), and with respect to claims 15 and 16, is said to teach that lauryl alcohol can be used as a polymerization initiator. Jarret et al. describe a block copolymer of caprolactone and *e.g.* lactide. Neither of these references addresses the fundamental deficiencies over the references to Li et al.

In view of the foregoing remarks, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Accordingly, Applicants request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

**CONCLUSION**

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 313632001000. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

Electronic signature: /Leslie A. Robinson/  
Leslie A. Robinson

Registration No.: 54,403  
MORRISON & FOERSTER LLP  
12531 High Bluff Drive, Suite 100  
San Diego, California 92130-2040  
(858) 314-7692